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Referee Commentaries

Re: Early prediction and aspirin for prevention of pre-eclampsia (EPAPP) study: a randomized controlled trial. A. O. Odibo, K. R. Goetzinger, L. Odibo and M. G. Tuuli. *Ultrasound Obstet Gynecol* 2015; **46**: 414–418.

In their study, Odibo *et al.* report the results of a randomized controlled trial (RCT) to estimate the efficacy of low-dose (81 mg) aspirin in preventing pre-eclampsia (PE) in women identified in the first trimester to be at high risk. Since PE is a major contributor to maternal and neonatal morbidity, prevention is extremely important. Women presenting for first-trimester ultrasound examination were recruited at $9+0$ to $13+6$ weeks and assessed for risk of PE based on a risk score that the authors had developed previously; the high-risk group was then randomized to receive the therapeutic intervention or placebo from $11+6$ to $13+6$ weeks until 37 weeks or delivery, whichever occurred first.

There are some notable problems with this trial. The study protocol initially included women who had a risk score >6 according to the authors' previously published risk-prediction system. Because of slow and inadequate recruitment, the inclusion criteria were then changed to recruit women who had any of the risk factors included in the risk score. However, the risk score that the authors used does not give equal weight to the factors included; for example, low pregnancy-associated plasma protein-A has a score of 1 while having chronic hypertension has a score of 4. By including women with any risk factor, the authors unify the weight of these risk factors and women are considered to be 'at high risk' equally, while, in fact, they constitute a heterogeneous group.

More importantly, as the authors acknowledge, the study was underpowered to detect the primary outcome. RCTs have the unique feature that if the sample size is sufficiently large, randomization distributes equally known and unknown confounders between the two groups[1]; this is not anticipated when sample sizes are small. This study was affected considerably by low participation rate and high drop-out rate, which are common threats to the internal validity of any RCT. As a consequence, the analysis was performed on an 'as-treated' rather than 'intention-to-treat' basis, which is inappropriate because the study groups are comparable only at randomization.

Finally, this RCT was terminated early because of lack of equipoise. Clinical equipoise, which is the ethical basis for the conduct and continuation of a randomized trial, is the genuine uncertainty regarding whether the treatment is beneficial. With the release of recommendations by the United States Preventive Task Force suggesting administration of aspirin in high-risk women, the authors considered continuation of the trial to be unethical. The recommendations were based on a recently published systematic review. One of the discussion points raised by the authors is whether evidence-based practice should rely on randomized trials or meta-analyses. The answer to this depends heavily on the quality of evidence synthesized or the characteristics of the RCT[2]. Observational studies have inherent potential for various biases that no statistical manipulation can eliminate, so their synthesis is not necessarily superior to a sufficiently large, properly conducted RCT.

These are common caveats that can render uninformative a well-designed randomized clinical trial. In summarizing the effect of all these problems, this clinical trial does not provide an answer to the question of whether high-risk pregnant women should take aspirin to prevent PE. However, as the authors conclude, it should form a useful basis for the design of future studies.

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